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Investigations of Hydrolytic Products of Butalbital

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Abstract □ Two pathways of cleavage of butalbital (5-allyl-5-isobutylbarbituric acid) were elucidated. Depending upon the reaction conditions, one or both routes might be operative. These proceed initially: (*a*) through 1,6-ring opening to the malonuric acid, and (*b*) *via* 1,2-cleavage of the barbiturate producing the diamide. Several intermediates were isolated and identified or characterized. At pH values around neutrality and a few units above, the hydrolysis takes place solely by means of the 1,6-solvolysis; at higher alkalinities (pH about 9.5), the 1,2-ring opening plays a role. Kinetics of acylureide breakdown at several hydrogen-ion concentrations and temperatures were studied. Data for the diamide and malonuric acid are reported. Ionic strength effects on the alkaline solvolysis of butalbital were examined. A positive relationship of the rate constant to the ionic strength was found, indicative of hydroxyl-ion attack on barbiturate monoanion as a mechanism of degradation.

Keyphrases □ Butalbital—intermediates, products of barbiturate-ring decomposition □ Barbituric acid derivatives—mechanism of butalbital degradation, ring cleavage □ Hydrolysis, butalbital—mechanism, intermediates, products □ Itobarbital—intermediates, products of barbiturate-ring decomposition

The kinetics of the degradation of butalbital[1] (itobarbital) were previously reported (1). However, nothing concerning the mode and products of the hydrolysis was available at that time.

This study pertains principally to the intermediates and final compounds related to decomposition of the barbiturate ring at pH > 7 because kinetics alone fail to illustrate the complete picture.

A review of barbiturate kinetics is available (2), as are several publications regarding decomposition products of barbiturates as their sodium salts (3–6). Conditions are variable between ambient (3) and reflux (4–6), with products dependent on structural considerations as well as pH. Little is available concerning the compounds formed by rupture of the pyrimidine ring as a function of changing pH.

The route of solvolysis of barbiturates has been postulated as passing through both 1,2- and 1,6-ring openings. In the case of butalbital, an investigation of the comparative importance of the two pathways was considered along with some kinetic aspects of the processes involved.

EXPERIMENTAL

Kinetic Procedures—A stock solution of sodium butalbital containing 542 mg. (0.0022 mole/100 ml.) was prepared using distilled water. Two-milliliter aliquots were placed in 200-ml. volumetric flasks, previously equilibrated at 80°, containing 198 ml. 0.05 *N* NaOH along with various quantities of sodium chloride. Ten-milliliter samples were withdrawn and read periodically against the appropriate blank at 240 nm. on a recording spectrophotometer[2] (1).

A stock solution of allylisobutylacetylurea containing 444 mg. (0.0022 mole/100 ml.) in ethanol or dioxane was prepared. Four-milliliter aliquots were placed in 200-ml. volumetric flasks, previously equilibrated at the specified temperatures. Samples were periodically withdrawn and read at 240 nm. against the appropriate blanks on the recording spectrophotometer.

The diamide was run in the same concentration as the acetylurea and barbiturate. It was followed spectrophotometrically at 240 nm.

A stock solution of allylisobutylmalonuric acid (10.6 mg./4 ml. ethanol) was prepared. Two milliliters was placed in 100 ml. of pH 7.0 phosphate and 9.2 borate buffer, μ = 0.10. Three-milliliter samples were withdrawn (adjusted to pH 11.5 with sodium hydroxide) and monitored periodically on the recording spectrophotometer at 240 nm.

Preparation of Hydrolytic Intermediates—*Allylisobutylacetylurea*—Ten grams of sodium butalbital was placed in 400 ml. phosphate buffer, giving a final measured pH of 8.5. The solution was heated at 80° for 48 hr., allowed to crystallize at room temperature, and filtered, yielding 2.3 g. (31.2%), m.p. 136–138° (3).

2-Allyl-2-isobutylmalonamide—One gram of sodium butalbital was heated for 24 hr. in 0.1 *N* NaOH, 80°, followed by extraction with 3 × 50 ml. portions of ether. The ether was allowed to evaporate slowly, yielding 15 mg., m.p. 213–215° (3).

Anal.—Calc. for $C_{10}H_{18}N_2O_2$: C, 60.6; H, 9.2; N, 14.1. Found: C, 60.3; H, 9.1; N, 13.8.

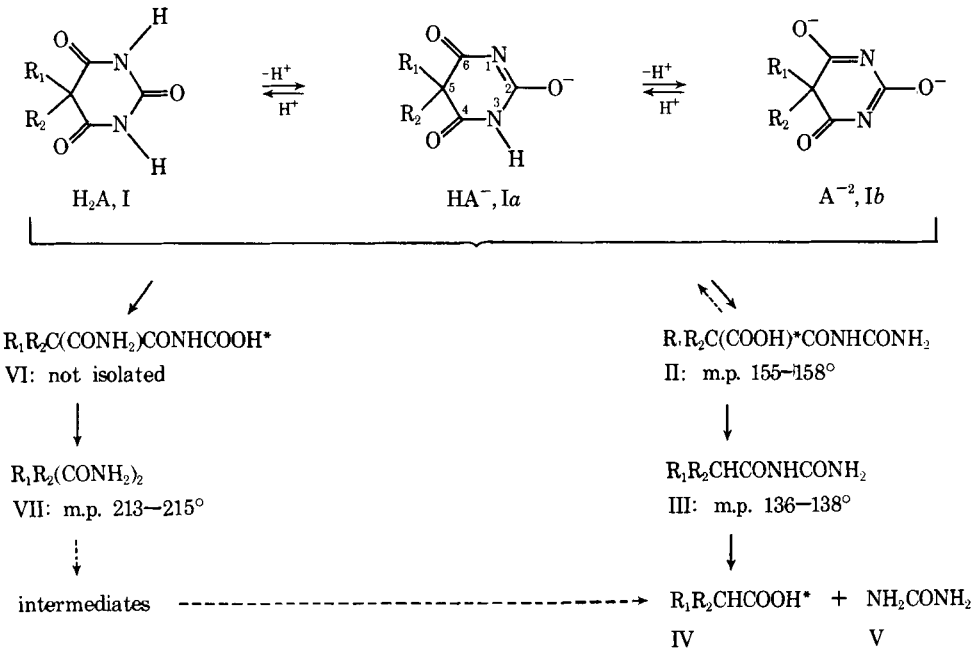
Allylisobutylmalonuric Acid—One gram of sodium butalbital was heated in pH 9 buffer for 48 hr. at 80°, allowed to cool, and filtered and the filtrate was made acidic, pH 4.5. The precipitate was collected after 3 days in the refrigerator, yielding 45 mg., m.p. 155–158°.

Anal.—Calc. for $C_{11}H_{18}N_2O_4$: C, 54.1; H, 7.5; N, 11.1. Found: C, 54.5; H, 7.5; N, 11.5.

Allylisobutylmalonic Acid—Fifty grams (0.16 mole) of barium hydroxide [$Ba(OH)_2 \cdot 8H_2O$] was dissolved in 300 ml. methanol and 96 ml. water with heating on a steam bath. The cloudy solution was

[1] Sandoptal.

[2] Cary 14.



Scheme I—Hydrolysis of butalbital in aqueous solution at pH 7 and above. Ia and Ib represent one of three possible structures of which two are the same for both Ia and Ib. At pH about 9, most of the barbiturate is in the form of HA⁻ (Ia); while at acidities above and below, significant amounts of either I or Ib are present. R_1R_2 = allyl, isobutyl. (Probably present as anions under reaction conditions employed.)*

filtered, the filtrate was reheated on a steam bath, and the resultant solution was combined with 39.5 g. (0.016 mole) diethyl allylisobutylmalonate[3] and warmed on a constant-temperature bath at 50° for 4 hr. with intermittent vigorous shaking. Filtration and drying produced 25.3 g. (0.077 mole) of barium allylisobutylmalonate.

A methanolic slurry of the barium salt (25.3 g., 0.077 mole) was slurried with 4.1 g. diatomaceous earth[4] and treated at 5° with dropwise addition of 95% sulfuric acid (4.2 ml.). The filtrate was removed *in vacuo*, and the residue was taken up in ether and dried overnight over anhydrous sodium sulfate. Evaporation of the ether yielded a solid which was recrystallized once from chloroform–petroleum ether, yielding 3.9 g., 24%, m.p. 98–102°.

Anal.—Calc. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 60.0; H, 8.4.

TLC—TLC was carried out on silica gel GF plates[5] of 250-μ thickness, spotted with 10–20 μl. of solution containing 5–10 mg./ml. solution. Chromatograms were run 15–17 cm. with a solvent system of isopropanol–chloroform–25% ammonium hydroxide (45:45:10). The barbiturate was visualized under short wavelength UV, while other spots were observed by means of iodine vapor. Urea was visualized utilizing 1% dimethylaminobenzaldehyde in ethanol followed by exposure to hydrogen chloride vapor (yellow spot) or 1% dimethylaminocinnamaldehyde in ethanol followed by exposure to hydrogen chloride vapor (red spot). Acidic components could be seen by means of bromcresol purple in ethanol (15 mg./100 ml.) where they gave a yellow coloration.

Identification of compounds was made by comparison of R_f values of authentic samples to reaction solutions spotted on the same plate. The following R_f values were determined using the isopropanol–chloroform–ammonia (45:45:10) solvent system: butalbital, 0.75; 2-allyl-2-isobutylmalonamide, 0.90; allylisobutylacetylurea, 0.95; urea, 0.30; allylisobutylacetic acid, 0.3; allylisobutylmalonuric acid, 0.35–0.40; and allylisobutylmalonic acid, 0.0. All except urea were observed on plates treated with iodine. Allylisobutylacetic acid and allylisobutylmalonuric acid, R_f 0.3–0.4, are not separable from one another by this solvent system but may be separated by running the plate a second time (two dimensionally) in chloroform–methanol (80:20) where the following R_f values were obtained: allylisobutylacetic acid, 0.75; and allylisobutylmalonuric acid, 0.3.

The products of the hydrolysis of the specific intermediates were noted by TLC, employing 5-mg./ml. solutions and spotting periodically along with known standards. Acylurea concentrations of this amount were obtained on inclusion of ethanol in the solvent. The diamide resisted dissolution in these or lower concentrations utilizing water-miscible solvents.

A solution of 2.5 mg./ml. allylisobutylacylurea was prepared with the aid of ethanol and heating at 80° in 0.1 *N* NaOH as well as pH 7 and 8 buffers. This solution was chromatographed using chloroform–isopropanol–ammonia followed by two-dimensional development using the previously mentioned chloroform–methanol system.

The malonic acid and the disubstituted acetic acid were chromatographed using chloroform–methanol–acetic acid (80:20:2), giving R_f values of 0.35 and 0.85, respectively. Visualization was by means of iodine vapor.

Buffer solutions, unless otherwise specified, were run at an ionic strength of 0.1. Alkali solutions were prepared by dilution of standardized sodium hydroxide with freshly boiled distilled water.

The pH values were determined on a pH meter[6] standardized with borate and phthalate buffers at the pertinent temperatures (7). The pH's of the sodium hydroxide solutions were calculated from activity coefficient data available in the literature (8).

RESULTS AND DISCUSSION

Barbituric acid derivatives, such as butalbital, are expected to decompose by two main pathways (Scheme I) in aqueous solution at neutrality and above (9–11). The first is through the malonuric acid, II, *via* the acetylurea[7], III, finally leading to the acetic acid, IV, and urea, V. The second mode is *via* the diamide, VII, through other intermediates, possibly producing IV and V. Several of these intermediates were isolated and studied individually. Fretwurst (3) reported the 1,6-opening as the predominant method of hydrolysis of the sodium salt of this barbituric acid in water.

The compounds listed in Scheme I, except VI, were characterized and/or isolated. Although VI is a precursor of VII, it is a carbamic acid derivative probably having a rather transitory existence in either the anionic or neutral form. Molecules of this structural type are not normally isolated as a consequence of this instability.

[3] Ganes Chemical Co., New York, N. Y.
[4] Celite.
[5] Analtech Inc., Newark, Del.
[6] Metrohm.
[7] Acylurea and acetylurea used interchangeably.

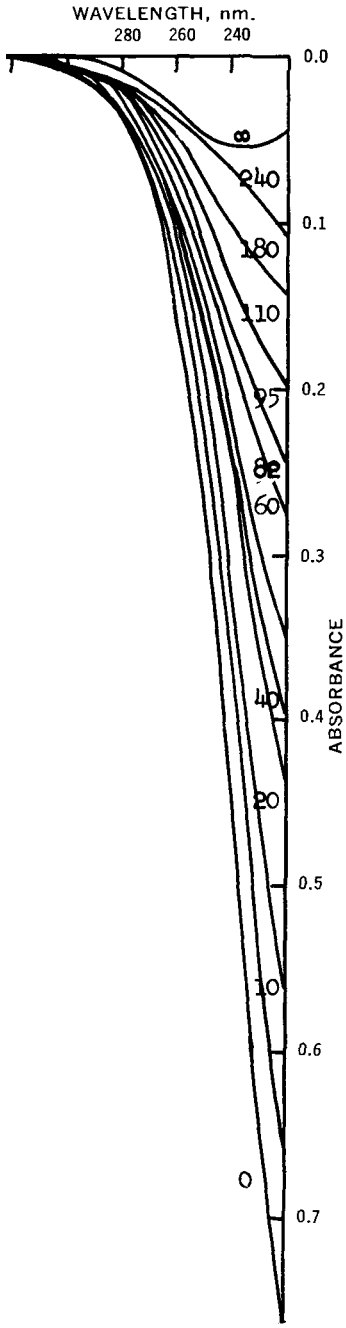


Figure 1—*Curve for absorbance diminution of 5-allyl-5-isobutylacylurea, III, in 2.2 × 10^{-4} M concentration as a function of time (minutes), 0.01 N NaOH, 80°. Time intervals indicated on curves in minutes, 240 nm. Residual absorbance = 0.05.*

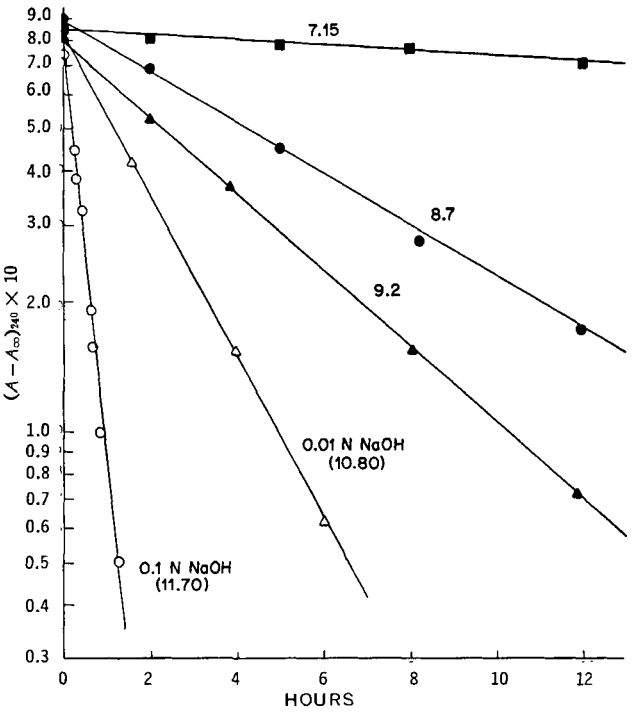


Figure 2—*Apparent first-order plots for decomposition of 2.2 × 10^{-4} M allylisobutylacetylurea at several pH values (Table I), 80°. Reaction followed by loss of absorbance at 240 nm. following adjustment of pH of samples to 11.5–11.7 with sodium hydroxide immediately prior to reading.*

The solvolysis of most barbituric acids closely resembles that of the 5-halouridines and 5-halouracils (9, 12, 13). Observed or apparent first-order rate constants may be estimated using the following expression:

$$\log (A - A_\infty) = \log (A_0 - A_\infty) - kt/2.303 \qquad \text{(Eq. 1)}$$

where A_0 is initial absorbance, A_∞ is residual absorbance, A is absorbance at any time t, and k is the observed or apparent first-order velocity constant (1).

Equation 1 also holds for decomposition of the acetylurea derived from butalbital where a concentration of 2.2 × 10^{-4} M results in A_0 = 0.36 (pH 11.5), with a residual absorbance, 0.048–0.052 (pH 11.5), 240 nm. No perturbation of the absorption spectrum was observed for the hydrolysis of the acylurea derivative. Table I illustrates the observed velocity constants for the various conditions under which hydrolysis of the acylurea was studied. The acylurea was found to cleave into urea and allylisobutylacetic acid with no formation of the amide corresponding to splitting of the NH—$CONH_2$ linkage (14). On TLC analysis of solutions of the acylurea only, spots indicative of the acetic acid and urea were seen. Figure 1 illustrates a typical first-order plot of loss of absorbance of the acylurea as a function of time.

Allylisobutylacetylurea, III, degrades at 20 times the rate of the barbiturate in 0.1 N NaOH (1); however, the barbiturate degrades about 10 times faster than the acetylurea at pH 7. This explains the isolation in rather high yield of the acylurea at pH 8.5, as seen in the *Experimental* section.

Figure 2 illustrates apparent first-order plots for degradation of allylisobutylacetylurea at various pH values, 80°. These data are similar to those previously reported for phenylethylacetylurea (10).

Arrhenius parameters concerned with the breakdown of the acetylurea are given in Fig. 3. Estimates of the apparent activation energies were made from the Arrhenius equation:

$$\log k_{obs} = \log P - E_a/2.303RT \qquad \text{(Eq. 2)}$$

Table I—Observed First-Order Rate Constants[a] (k, hr.$^{-1}$) for Breakdown of Allylisobutylacetylurea (2.2 × 10^{-4} M) in Aqueous Solution[b]

Buffers[c]							
[Na-H_2PO_4]	[Na_2-HPO_4]	pH[d,e]	60°	pH[d,e]	70°	pH[d,e]	80°
0.02	0.058	7.18	0.0006	7.15	0.0010	7.14	0.0017
[H_3BO_3]	[NaOH]						
0.05	0.021	8.8	0.0027	8.7	0.0061	8.65	0.0131
0.05	0.037	9.25	0.0043	9.2	0.0081	9.2	0.0186
—	0.01	11.02	0.126	10.80	0.425	10.30	0.98
—	0.10	11.90	1.12	11.70	2.92	11.49	6.39

[a] Rate constants reproducible ± 15% at 240 nm. Additional rate constants, 50°: 0.1 N NaOH, 0.47; 0.01 N NaOH, 0.041; pH 9.25, 0.0016; pH 8.8, 0.0010; pH 7.12, 0.00028. [b] Ionic strength constant at 0.1 by addition of sodium chloride. [c] $NaH_2PO_4 \cdot H_2O$ and $Na_2HPO_4 \cdot 7H_2O$ hydrated forms used as buffers. [d] pH values obtained from Metrohm pH meter calibrated at specified temperatures. [e] pH values of sodium hydroxide solutions calculated from $pK_w - pOH$ = pH, where pOH = log [NaOH)·$\gamma\pm$.

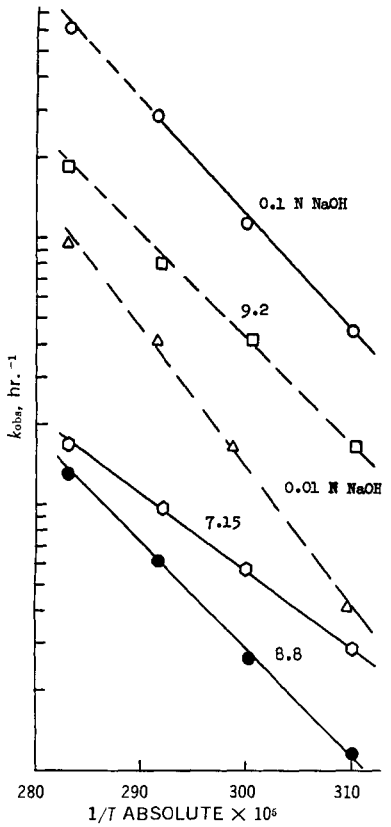


Figure 3—*Arrhenius plots for hydrolysis of allylisobutylacetylurea at various hydrogen-ion concentrations. The pH values are indicated on figure.*

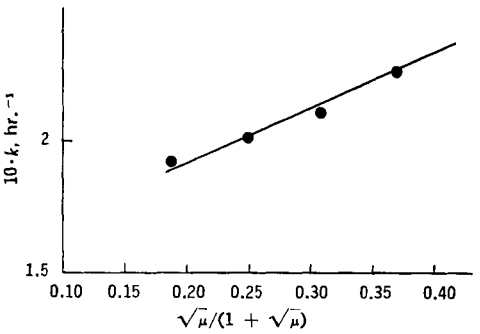


Figure 4—*Effect of ionic strength on hydrolysis of 2.2 × 10^{-4} M sodium butalbital at pH 11.2 (0.05 N NaOH) at 80° with ionic strength increased by addition of sodium chloride. Samples were withdrawn periodically and monitored at 240 nm. Apparent or observed first-order rate constants are plotted on the ordinate against a function of the ionic strength on the abscissa.*

Values derived from the preceding expression vary from 13.0 to 22.0 kcal./mole under the conditions investigated.

The larger apparent energies, or situation, for the more basic solution (Fig. 3) may be the consequence of enhanced energetic requirements for hydroxyl-ion attack on anionic acylurea at high pH values relative to hydroxyl-ion reaction with the neutral acylurea molecules at lower pH values.

The symmetrical diamide (Compound VII, Scheme I) was prepared in minute amounts by heating the sodium barbiturate in 0.1 *N* NaOH; it was previously reported by Fretwurst (3). This compound was observed only at pH values of 9–9.5 and above. Its formation is seemingly in minimal amounts relative to the acylurea.

The allylisobutylmalonuric acid (Compound II, Scheme I) was produced by heating pH 9.0 solutions of the barbiturate followed by adjustment of the pH to 4.5 after removal of the diacetylurea and unreacted barbiturate present. This compound, m.p. 155–158°, gave mass spectral, NMR, and elemental analyses indicative of the malonuric acid. It is the expected intermediate in formation of the acylurea, III. Diethylmalonuric acid was previously isolated as a degradative intermediate of barbital (3, 9).

Compound III produced acylurea was well as urea and the corresponding acetic acid, IV, on hydrolysis as 0.1 *N* NaOH. These hydrolytic products were observed on TLC plates.

Allylisobutylmalonic acid was postulated as a decomposition product of the diamide, VII, with subsequent production of carbon dioxide as well as allylisobutylacetic acid in alkaline media. This previously unreported malonic acid was prepared by hydrolysis of the diethyl ester in methanolic barium hydroxide followed by treatment with sulfuric acid to remove the barium present[8]. The acid, m.p. 98–102°, was produced in 24% yield. It exhibited R_f values dissimilar to any compounds present in the hydrolysis media of the barbiturate in the range of pH values investigated. From these TLC analyses, it was concluded that the malonic acid is no more than a transitory intermediate in decomposition of the diamide, although its possible presence cannot be discounted.

It has been postulated that the pathway leading through the diamide, VII, may be a route of decomposition of uncharged barbiturate, I, while the route through the malonuric acid, II, and acetylurea, III, serves as a method of breakdown of the ionic species, Ia (12). Garrett *et al.* (9) showed that an equilibrium between diethylmalonuric acid and barbital (diethylbarbituric acid) exists. As a consequence of this recycling, the 1,2-cleavage may not be a result of specific attack on neutral barbiturate as much as a consequence of the equilibrium at various pH values (9). The malonuric acid, m.p. 155–158°, was monitored at 80°, 240 nm., giving a $t_{1/2}$ = 56 hr. at pH 9.2 as measured by absorbance loss. At pH 7, absorbance increased up to 67 hr. followed by a slow diminution. The results at pH 7 are rather analogous to those reported by Garrett *et al.* (9).

With butalbital, no measurable amounts (TLC) of the diamide were found at pH < 9.5, 80°. At moderate alkalinity (pH 7–9.5), the products and intermediates of the barbiturate hydrolysis were allylisobutylmalonuric acid, allylisobutylacetylurea, allylisobutylacetic acid, and urea (Compounds II–V, Scheme I).

At higher pH values, about 9.5 and greater, 80°, the diamide and a second spot, R_f about 0.2, were noted.

The diamide was monitored at 240 nm., 80°, in 0.1 *N* NaOH with a resultant k = 0.20 hr.$^{-1}$, $t_{1/2}$ = 3.5 hr.

The significance of finding 1,2- or its equivalent 2,3-splitting only at higher hydroxyl-ion concentrations is that the likelihood of hydroxide or water reacting with the neutral species is low. The same holds for hydroxyl ion with dianionic butalbital, because little is produced up to pH 9.5 where mainly the monoanionic form occurs. It, therefore, appears that the diamide, VII, may be the result of a solvent reaction with dianionic species since this doubly negatively charged molecule exists in appreciable amounts at pH 9.5 and above, pK_{a_2} 11.6, 80°. Hydroxide reaction with the dianionic species may not be favored due to repellent forces between negative and double negative charges of the two ions but cannot be discounted. On the basis of presently available information, assignment cannot be made exclusively to solvent or hydroxide.

The symmetrical diamide was formed in what appeared to be relatively low amounts. Attempted quantitative isolation by classical methods proved tedious and was not pursued.

Bulky substituents at the 5-position led to increased production of the diamide, as pointed out in the work of Fretwurst (3) and Aspelund (4). This is obviously a steric factor.

In the cases studied, 1,6-cleavage was always the predominant route of decomposition. However, 1,2-cleavage of butalbital is probably the result of a reaction of the dianionic species since no diamide is formed at pH values below 9.5 where there is a preponderance of monoanionic and neutral barbiturate.

Decomposition of Barbiturate Ring—Kinetics of the parent barbiturate pyrimidine ring may be explained by two kinetically equivalent relationships (1):

$$k_{obs} = k''_{H_2O} f_{A^{2-}} + k'_{H_2O} f_{HA^-} \qquad \text{(Eq. 3)}$$

[8] Personal communication, Dr. H. Dugger, Sandoz-Wander, Hanover, N. J.

or:

$$k_{obs} = k'_{OH^-}[OH^-]f_{HA^-} + k_{OH^-}[OH^-]f_{H_2A} \quad \text{(Eq. 4)}$$

where f_{H_2A}, f_{HA^-}, and $f_{A^{2-}}$ are fractions of barbiturate in the neutral, monoanionic, and dianionic states, respectively. The specific catalytic constants are indicated as k''_{H_2O}, k'_{H_2O}, k_{OH^-}, and k'_{OH^-}, respectively, for water and hydroxide-ion attack.

Ionic Strength Effects—Perturbation of the apparent first-order rate constant was noted on alteration of the ionic strength of solutions containing the barbiturate (Fig. 4). This was previously done (1) and slight effects were noted. Utilization of the extended Debye-Hückel equation in conjunction with the Brönsted-Bjerrum equation results in the expression (15):

$$\log k_{obs} = \log k_0 + 2Qz_az_b\frac{\sqrt{\mu}}{1+\sqrt{\mu}} \quad \text{(Eq. 5)}$$

When the log of the apparent or observed first-order rate constant, k_{obs}, is plotted against $\sqrt{\mu}/(1+\sqrt{\mu})$, a graph with slope 0.75 is obtained (Fig. 2). The term k_0 is the rate constant where ionic strength $\mu = 0$. The value for the constant $2Q$ at 80° is 1.15 (15, 16), and the positive slope is indicative of an interaction of two like charged ions, z_az_b, namely OH^- and HA^-, leading to hydrolysis in 0.05 *N* NaOH (pH 11.2). At this pH the barbituric acid is 75% in the monoanionic form: pKa_2 11.6, pKa_1 7.6 (1).

TLC Techniques—The chloroform–isopropanol–ammonia system listed in the *Experimental* section is a standard for separation of barbiturates and proved most satisfactory for differentiation of butalbital from its hydrolytic products. Silica gel GF plates[5] were employed with the intact barbiturate visualized under short wavelength UV light. Degradation products were visualized on a treatment of iodine vapor following development of the chromatogram. Urea could be visualized by means of dimethylaminobenzaldehyde or dimethylaminocinnamaldehyde followed by hydrogen chloride vapor giving yellow and red colorations, respectively.

The malonuric acid was studied by periodically spotting 20 μl. of 0.5% aqueous solutions at various pH values. The corresponding acylurea, acetic acid, and urea were noted on visualization. As the malonuric and acetic acids overlapped, they could be separated by a two-dimensional procedure using chloroform–methanol (80:20) following the primary development.

The acetylurea produced only the acetic acid and urea when 5% solutions in aqueous ethanol were examined. The ethanol was necessary for solubilization of the acetylurea.

SUMMARY

Degradation of butalbital was studied in aqueous solution from pH 7 to 1.0 *N* NaOH in the temperature range of 60–80°. The hydrolysis products were characterized with emphasis on the two plausible pathways of decomposition of the pyrimidine ring relative to the point of cleavage.

Ionic strength effects indicate OH-attack on barbituate monoanion as a primary route of decomposition at certain pH values.

The barbiturate ring was found to break principally at the 1,6- or equivalent 3,4-positions in the region around neutrality. At higher pH values (pH > 9.5), some 1,2- or 2,3-cleavage takes place, leading to the diamide. It appears that production of the acylurea is the predominant route of decomposition under the conditions examined, with 1,2-cleavage being ancillary at higher alkalinities.

The acylurea was found to degrade rapidly at low hydrogen-ion concentrations, with the reaction velocity being slow relative to the barbiturate at pH 7. This allowed isolation of the compound at pH 8.5.

The malonuric acid and diamide produced by the hydrolysis were both prepared and identified.

Methods for separating the reaction products in the reaction mixture by TLC as well as techniques for visualizing these substances were discussed.

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